Routine Aspirin or Nonsteroidal Anti-inflammatory Drugs for the Primary Prevention of Colorectal Cancer: U.S. Preventive Services Task Force Recommendation Statement

U.S. Preventive Services Task Force*

This statement summarizes the U.S. Preventive Services Task Force (USPSTF) recommendation and supporting scientific evidence on routine use of aspirin or nonsteroidal anti-inflammatory drugs for the primary prevention of colorectal cancer. The complete information on which this statement is based, including evidence tables and references, is available in the accompanying articles in this issue and on the USPSTF Web site (www.preventiveservices.ahrq.gov).

The USPSTF is redesigning its recommendation statement in response to feedback from primary care clinicians. The USPSTF plans to release, later in 2007, a new, updated recommendation statement that is easier to read and incorporates advances in USPSTF methodology. The recommendation statement below is an interim version that combines existing language and elements with a new format. Although the definitions of grades remain the same, other elements have been revised.

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*For a list of the members of the U.S. Preventive Services Task Force, see the Appendix (available at www.annals.org).

Summary of Recommendation

The USPSTF recommends against the routine use of aspirin and nonsteroidal anti-inflammatory drugs (NSAIDs) to prevent colorectal cancer in individuals at average risk for colorectal cancer. This is a **grade D** recommendation. (See **Appendix Table 1** for a description of the USPSTF classification of recommendations and **Appendix Table 2** for a description of the USPSTF classification of levels of evidence. Both are available at www.annals.org.)

Rationale

Importance:

Colorectal cancer represents the third most common type of cancer in both men and women and is the second leading cause of cancer-related deaths in the United States.

Recognition of risk status:

The vast majority of cases of colorectal cancer arise from adenomatous polyps in average-risk individuals older than 50 years of age.

Benefits of aspirin and NSAID use:

There is fair to good evidence that aspirin and NSAIDs, taken in higher doses for longer periods, reduces the incidence of adenomatous polyps.

There is good evidence that low-dose aspirin does not lead to a reduction in the incidence of colorectal cancer.

There is fair evidence that aspirin used in doses higher than those recommended for prevention of cardiovascular disease and NSAIDs may be associated with a reduction in the incidence of colorectal cancer.

There is fair evidence that aspirin used over longer periods may be associated with a reduction in the incidence of colorectal cancer.

There is poor-quality evidence that aspirin and NSAID use leads to a reduction in colorectal cancer–associated mortality.

Harms of aspirin and NSAID use:

There is good evidence that aspirin increases the incidence of gastrointestinal bleeding in a dose-related manner and fair evidence that aspirin increases the incidence of hemorrhagic stroke.

There is good evidence that NSAIDs increase the incidence of gastrointestinal bleeding and renal impairment, especially in the elderly.

There is good evidence that cyclooxygenase-2 inhibitors, a class of NSAID, increase the incidence of renal impairment. Cyclooxygenase-2 inhibitors appear to be associated with an increased risk for cardiovascular events.

Overall, there is good evidence of at least moderate harms associated with aspirin and NSAIDs.

See also:

Print

Related articles 365, 376
Summary for Patients I-35

Web-Only

Appendix
Appendix Tables
Conversion of tables into slides

USPSTF assessment:

Overall, the USPSTF concluded that harms outweigh the benefits of aspirin and NSAID use for the prevention of colorectal cancer.

Clinical Considerations

This recommendation applies to asymptomatic adults at average risk for colorectal cancer, including those with a family history of colorectal cancer, and not to individuals with familial adenomatous polyposis, hereditary nonpolyposis colon cancer syndromes (Lynch I or II), or a history of colorectal cancer or adenomas.

Clinicians should continue to discuss aspirin chemoprophylaxis with patients who are at increased risk for coronary heart disease, but there is good evidence that low-dose aspirin used to prevent coronary heart disease (CHD) events in those at increased risk for CHD does not lead to a reduced incidence of colorectal cancer. Aspirin use by patients at increased risk for coronary heart disease has been shown to reduce all-cause mortality. The evidence and recommendation statements from the USPSTF for aspirin chemoprophylaxis can be found on the AHRQ Web site (www.preventiveservices.ahrq.gov).

More than 80% of colorectal cancers arise from adenomatous polyps. However, most adenomatous polyps will not progress to cancer. Age represents a major risk factor for colorectal cancer, with approximately 90% of cases occurring after age 50 years. Thirty to fifty percent of Americans older than age 50 will develop adenomatous polyps. Between 1% and 10% of these polyps will progress to cancer in 5 to 10 years. The risk for a polyp developing into cancer depends on the villous architecture, degree of cytologic dysplasia, size, and total number of polyps.

All persons older than age 50 who are at average risk for colorectal cancer should be screened for colorectal cancer regardless of their aspirin or NSAID use. The USPSTF recommendation on screening for colorectal cancer can be accessed at www.preventiveservices.ahrq.gov.

Discussion

Burden of Illness

While colorectal cancer represents the third most common cause of cancer and has the second highest mortality rate among cancers, incidence is decreasing. Progress in earlier detection and removal of precancerous polyps through screening, in addition to improved therapies, may account for the decreasing mortality rate (1–5). The lifetime risk for colorectal cancer in the general population is about 5% to 6% (6), and most cases occur after age 50. The incidence of colorectal cancer is influenced by family history. People who have 2 or more first- or second-degree relatives (or both) with colorectal cancer represent approximately 20% of all people with colorectal cancer (7). About 5% to 10% of all cases of colorectal cancer develop in people with the autosomal dominant conditions of familial adenomatous polyposis or hereditary nonpolyposis colorectal cancer, also known as the Lynch syndrome (8). Despite reductions in incidence of colorectal cancer in all races, racial and ethnic disparities in incidence and mortality from colorectal cancer remain. African Americans have higher colorectal cancer incidence and mortality rates than all other races (2).

Scope

The USPSTF reviewed the evidence on the effect of aspirin and NSAID use on colorectal cancer incidence and mortality. It reviewed the evidence on the efficacy of aspirin and NSAIDs in reducing colorectal adenoma and cancer incidence, colorectal cancer mortality, and all-cause mortality, including the dose-dependent effects on these outcomes, and the harms associated with aspirin and NSAID use in healthy adults.

Effectiveness of Aspirin and NSAID Use

Colorectal Cancer Incidence

On the basis of randomized, controlled trials (RCTs), cohort studies, and case–control studies, the USPSTF found good evidence that low-dose aspirin does not lead to a reduction in the incidence of colorectal cancer, fair evidence that higher-dose aspirin and NSAIDs may be associated with a reduction in the incidence of colorectal cancer, and fair evidence that aspirin used over longer periods may be associated with a reduction in the incidence of colorectal cancer.

The Women's Health Study and the Physicians' Health Study, both good-quality RCTs, assessed the efficacy of low-dose aspirin use (100 mg every other day and 325 mg every other day) in decreasing colorectal cancer incidence and found no improvement in colorectal cancer incidence (9, 10).

The Nurses' Health Study, a good-quality cohort study, found a duration- and dose-dependent response: A significant benefit in colorectal cancer reduction was not found until more than a decade of use, and maximum risk reduction for colorectal cancer occurred at a high dose of aspirin (more than fourteen 325-mg aspirin tablets per week). Nurses who took more than 14 aspirin tablets per week for longer than 10 years had a colorectal cancer relative risk (RR) of 0.47 (95% CI, 0.31 to 0.71) (11). Two case–control studies (12, 13) assessed the effect of aspirin dosing on colorectal cancer incidence and found that only the highest dose of aspirin (for example, 300 mg and 325 mg per day) in each study resulted in a statistically significant reduction in colorectal cancer incidence: RR, 0.60 (CI, 0.5 to 0.9) (12); RR, 0.60 (CI, 0.4 to 0.9) (13).

No RCT examined the effect of NSAIDs on colorectal cancer incidence. One fair-quality cohort study (14) assessed the effect of NSAIDs on colorectal cancer incidence and found that patients using NSAIDs for more than 12 months at a moderate dosage (defined as a dosage between the minimum and maximum recommended dosages) showed a reduction in colorectal cancer incidence (RR,

0.59 [CI, 0.45 to 0.77]). Four pooled case–control studies of varying quality (13, 15–17) showed that regular use of NSAIDs was associated with reductions in colorectal cancer incidence (RR, 0.70 [CI, 0.63 to 0.78]). One poor-quality case–control study (18) found that moderate and high calculated cumulative dosing (≥320 mg) of "any NSAID" was associated with statistically significant reductions in colorectal cancer incidence (RR for moderate dosing, 0.19 [CI, 0.09 to 0.52]; RR for high dosing, 0.22 [CI, 0.09 to 0.56]).

While not the focus of this recommendation, the USPSTF assessed the magnitude of effect of aspirin and NSAID use on the incidence of colorectal adenomas because adenomatous polyps give rise to most cases of colorectal cancer. There is fair- to good-quality evidence that aspirin and NSAID use decreases the incidence of colorectal adenomas. The Physician's Health Study assessed the efficacy of low-dose aspirin use in decreasing colorectal adenomas and found no improvement in the incidence of colorectal adenomas (10). The Nurses' Health Study assessed the efficacy of low-dose aspirin in decreasing colorectal adenomas and found a statistically significant reduction in the incidence of colorectal adenomas, in which a higher aspirin dose conferred a greater relative risk reduction (19). Four pooled case–control studies of poor to good quality found that regular use of NSAIDs was associated with significant reductions in incidence of colorectal adenomas (20–23).

Colorectal Cancer Mortality

Based on a limited number of studies addressing the efficacy of aspirin and NSAID use on the reduction of colorectal cancer mortality, the USPSTF concluded that there is poor-quality evidence that aspirin and NSAID use leads to a reduction in colorectal cancer mortality. The Women's Health Study, a good-quality RCT, found that a decade's use of low-dose aspirin in healthy women had no effect on colorectal cancer mortality (9). One fair-quality cohort study (24) revealed a significant decrease in colorectal cancer mortality following low-dose aspirin administration (RR, 0.58 [CI, 0.38 to 0.97]). No RCT examining the effect of NSAIDs on colorectal cancer mortality was found. One fair-quality cohort study that examined the effect of NSAIDs on colorectal cancer mortality found no reduction in this outcome (25).

Harms

The USPSTF found good-quality evidence that aspirin increases the incidence of gastrointestinal bleeding in a dose-related manner and fair evidence that aspirin increases the incidence of hemorrhagic stroke. A meta-analysis (26) of 21 RCTs that included all randomized, placebo-controlled trials listed in the Anti-platelet Trialists Collaboration, in which a direct aspirin–placebo comparison was possible, found a pooled odds ratios (OR) of 1.5 to 2.0 for categories of gastrointestinal bleeding with aspirin use (for example, hematemesis and melena). A meta-analysis (27) of 16 RCTs (14 secondary prevention and 2 primary prevention trials) found that aspirin treatment was also associated with an absolute risk increase in hemorrhagic stroke of 12 events per 10 000 persons (CI, 5 to 20 events; $P < 0.001$). However, a meta-analysis (28) of 5 primary prevention RCTs examining aspirin chemoprevention in patients without previously known cardiovascular disease found that aspirin contributed to a nonsignificant increased risk for hemorrhagic stroke (summary OR, 1.4 [CI, 0.9 to 2.0]).

There is good-quality evidence on the harms of NSAIDs. A meta-analysis (29) of gastrointestinal complications of NSAIDs from 16 RCTs, most of which are good-quality studies, found an OR of 5.36 (CI, 1.79 to 16.1) for perforations, ulcers, and bleeding. A meta-analysis (30) of 9 RCTs that compared the efficacy and safety of valdecoxib with those of NSAIDs or placebo in individuals with active osteoarthritis or rheumatoid arthritis found a statistically significant higher rate of clinically significant renal events for valdecoxib and NSAIDs (2% to 3%) compared with placebo (0.8%). A nested case–control study (31) using Tennessee Medicaid enrollees age 65 years or older who had been hospitalized with community-acquired acute renal failure found that, after adjustment for demographic factors and comorbidity, use of NSAIDs increased the risk for acute renal failure by 58% (adjusted OR, 1.58 [CI, 1.34 to 1.86]). A meta-analysis (32) of 50 RCTs found that NSAIDs elevated supine mean blood pressure by 5.0 mm Hg (CI, 1.2 to 8.7 mm Hg).

Recommendations of Others

The American Cancer Society currently does not recommend aspirin or NSAID use to prevent colorectal cancer because of potential side effects, especially gastrointestinal bleeding (33). The American Gastroenterological Association, the American College of Gastroenterology, the American College of Physicians, the American Medical Association, and the National Institutes of Health offer no recommendations regarding the use of aspirin or NSAIDs for colorectal cancer prevention.

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Requests for Single Reprints: Reprints are available from the USPSTF Web site (www.preventiveservices.ahrq.gov) and in print through the Agency for Healthcare Research and Quality Publications Clearinghouse (800-358-9295).

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Appendix: U.S. Preventive Services Task Force

Members of the U.S. Preventive Services Task Force† are Ned Calonge, MD, MPH, *Chair* (Colorado Department of Public Health and Environment, Denver, Colorado); Diana B. Petitti, MD, MPH, *Vice Chair* (Kaiser Permanente Southern California, Pasadena, California); Thomas G. DeWitt, MD (Children's Hospital Medical Center, Cincinnati, Ohio); Leon Gordis, MD, MPH, DrPH (Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland); Kimberly D. Gregory, MD, MPH (Cedars-Sinai Medical Center, Los Angeles, California); Russell Harris, MD, MPH (University of North Carolina School of Medicine, Chapel Hill, North Carolina); Kenneth W. Kizer, MD, MPH (National Quality Forum, Washington, D.C.); Michael L. LeFevre, MD, MSPH (University of Missouri School of Medicine, Columbia, Missouri); Carol Loveland-Cherry, PhD, RN (University of Michigan School of Nursing, Ann Arbor, Michigan); Lucy N. Marion, PhD, RN (Medical College of Georgia, Augusta, Georgia); Virginia A. Moyer, MD, MPH (University of Texas Health Science Center, Houston, Texas); Judith K. Ockene, PhD (University of Massachusetts Medical School, Worcester, Massachusetts); George F. Sawaya, MD (University of California, San Francisco, San Francisco, California); Albert L. Siu, MD, MSPH (Mount Sinai Medical Center, New York, New York); Steven M. Teutsch, MD, MPH (Merck & Company, Inc., West Point, Pennsylvania); and Barbara P. Yawn, MD, MSc (Olmsted Research Center, Rochester, Minnesota).

†This list includes members of the Task Force at the time of final approval of this recommendation. For a list of current Task Force members, go to www.ahrq.gov/clinic/uspstfab.htm. Steven M. Teutsch, MD, MPH, recused himself from voting on this topic.

Appendix Table 1. **U.S. Preventive Services Task Force Recommendations and Ratings***

Grade	Recommendation
A	The USPSTF strongly recommends that clinicians provide [the service] to eligible patients. *The USPSTF found good evidence that [the service] improves important health outcomes and concludes that benefits substantially outweigh harms.*
B	The USPSTF recommends that clinicians provide [the service] to eligible patients. *The USPSTF found at least fair evidence that [the service] improves important health outcomes and concludes that benefits outweigh harms.*
C	The USPSTF makes no recommendation for or against routine provision of [the service]. *The USPSTF found at least fair evidence that [the service] can improve health outcomes but concludes that the balance of benefits and harms is too close to justify a general recommendation.*
D	The USPSTF recommends against routinely providing [the service] to asymptomatic patients. *The USPSTF found at least fair evidence that [the service] is ineffective or that harms outweigh benefits.*
I	The USPSTF concludes that the evidence is insufficient to recommend for or against routinely providing [the service]. *Evidence that [the service] is effective is lacking, of poor quality, or conflicting, and the balance of benefits and harms cannot be determined.*

* The U.S. Preventive Services Task Force (USPSTF) grades its recommendations according to 1 of 5 classifications (A, B, C, D, I) reflecting the strength of evidence and magnitude of net benefit (benefits minus harms).

Appendix Table 2. **U.S. Preventive Services Task Force Grades for Strength of Overall Evidence***

Grade	Definition
Good	Evidence includes consistent results from well-designed, well-conducted studies in representative populations that directly assess effects on health outcomes.
Fair	Evidence is sufficient to determine effects on health outcomes, but the strength of the evidence is limited by the number, quality, or consistency of the individual studies; generalizability to routine practice; or indirect nature of the evidence on health outcomes.
Poor	Evidence is insufficient to assess the effects on health outcomes because of limited number or power of studies, important flaws in their design or conduct, gaps in the chain of evidence, or lack of information on important health outcomes.

* The U.S. Preventive Services Task Force (USPSTF) grades the quality of the overall evidence for a service on a 3-point scale (good, fair, poor).